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NEUROLOGICAL ASSESSMENT OF HEMODIALYSIS PATIENTS A SINGLE CENTER STUDY

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ABSTRACT

Background Neurological impairment in patients with chronic kidney disease remains an important source of morbidity and mortality. Hemodialysis patients have not fully corrected neurological manifestations. This study was designed to conduct the prevalence of neurological manifestations among adult hemodialysis patients seen in the Nephrology center of Medical City- Baghdad Teaching Hospital in the period from November 2011 to November 2012.

Patients and Methods This was a prospective cross-sectional hospital based study. One hundred and four adult hemodialysis patients were included in the study using a simple, direct standardized questionnaire including history, systemic, neurological examinations, body weight and investigations like: Blood urea, serum creatinine, PCV%, and electrolytes.

Results: Neurological disorders are common among patients on hemodialysis where weakness was the most common symptom and fine tremor was the most common sign. Most of the patients enrolled in the study had partially dependent gait. The duration that the patient is on hemodialysis has a negative impact, and the neurological symptoms like headache, insomnia, fine tremor, proximal myopathy, distal myopathy, muscle cramps, weak/absent reflexes, peripheral neuropathy, postural hypotension, abnormal valsalva, nocturnal/post-prandial diarrhea and dependent gait were more common in patients whose spent more than one year on hemodialysis and the difference was statistically significant. The body mass index can affect some of the neurological manifestations and our study shows that there was a statistically significant difference in proximal weakness, distal weakness, weak/absent reflexes, peripheral neuropathy, postural hypotension, abnormal valsalva, dependent gait and partially dependent gait which are presented more in patients with BMI < 18.5 kg/m^2. Patients with anemia (Hb<10 gm/dl) had more postural hypotension than those with (Hb>10 gm/d) and the difference statistically was significant while other neurological manifestations not. The hepatitis state of the patient has no impact on the neurological manifestations of the patients.

KEYWORDS: Hemodialysis, Neurological, Neuropathy, Patients, Chronic Kidney Disease & Uremic Syndrome

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Original Article

INTRODUCTION

Neurologic aspects of chronic kidney disease encompass a diverse spectrum of clinical disorders and syndromes. Indeed, clinical uremia was first described principally as a neurologic illness manifested by disturbances of cognitive, somatosensory, neuromuscular, and autonomic dysfunction. Renal replacement therapy attenuates these features of the uremic syndrome, suggesting a central role for a retained solute (or solutes) in the pathogenesis of the neurologic manifestations of uremia[(1)] In addition, disorders of the nervous system are associated with renal disease in patients with systemic disorders (e.g., hypertensive encephalopathy, thrombotic

microangiopathies, atheroembolic and atherosclerotic disease, vasculitides), fluid and electrolyte abnormalities, and multisystem disease in the intensive care unit setting.[2]

Uremic syndrome can cause:

- Disorders of cognitive function.
- Neuropathies.
- Sleep disorders.

Disorder of Cognitive Function

It includes:

- Delirium.
- Chronic cognitive impairment among persons with CKD and ESRD.

Delirium

It is an acute confessional state characterized by a recent onset of fluctuating awareness, impairment of memory and attention, and disorganized thinking that can be attributable to a medical condition, intoxication, or medication side effect.[1] In uremic patients, it can be classified into: Uremic encephalopathy and Dysequilibrium syndrome.

- **Uremic Encephalopathy:** It is a syndrome of delirium seen in untreated or inadequately treated ESRD which involves a spectrum of brain abnormalities that may clinically range from nearly imperceptible changes to coma.[2]
- **Dysequilibrium Syndrome:** The syndrome is believed to be caused by brain swelling due to a lag in osmolar shifts between blood and brain during dialysis, but changes in brain pH may also play a role. Disequilibrium is more likely to occur when patients with advanced states of uremia are dialyzed for excessive lengths of time during their first treatment sessions.

Chronic Cognitive Impairment among Persons with CKD and ESRD

It is a chronic confusional state characterized by impairment in memory and at least one other cognitive domain, such as language, orientation, reasoning, or executive functioning. There are two types of chronic cognitive impairment:

- **Dialysis Dementia:** It occurred almost exclusively among patients on hemodialysis rather than peritoneal dialysis [6]. It is probably a multi-factorial syndrome occurring in sporadic, endemic and epidemic types. In particular, in the epidemic type, aluminum-based phosphate binders are considered to be major causes.[7]With the almost universal preparation of dialysate water by reverse osmosis and the marked reduction in aluminum-containing the phosphate binder use, aluminum-induced encephalopathy has virtually disappeared.
- **Chronic Cognitive Impairment:** In the general population, Alzheimer's dementia accounts for 60% to 80% of cases of dementia, vascular dementia for 10% to 20%. In the ESRD population, vascular dementia may be much more prominent than in the general population.[8]

Neuropathy

- **Peripheral Neuropathy:** It is a distal, symmetric, mixed sensorimotor poly-neuropathy. It typically involves the lower extremities more often than the upper extremities, and sensory symptoms precede motor symptoms. The pathophysiologic process of polyneuropathy involves axonal degeneration in a length-dependent fashion. Primary demyelinating neuropathies are rare in the context of CKD except when the renal disease is the result of an illness that also causes demyelination (e.g., multiple myeloma).[(2)]According to the middle molecule hypothesis, accumulated toxins in the range of 300 to 12,000 d, including peptide hormones and polyamines, may lead to progression of neuropathy in HD patients.[(9).] Polyneuropathies occur in about two thirds of uremic patients and may progress rapidly in advanced CKD.

- **Mononeuropathy:** Mononeuropathy syndromes typically involve compression or ischemia of the ulnar or median nerves and are most often attributable to dialysis-associated amyloidosis or ischemic mononeuropathy associated with an arteriovenous fistula.(1)Occasionally, prolonged recumbency during the hemodialysis procedure leads to ulnar and peroneal nerve palsies.(5). Mononeuritis multiplex should raise the question of vasculitic neuropathy.(11)

- **Autonomic Neuropathy:** Autonomic neuropathy is due to axonal disease and thus is length dependent. For that reason, the longest autonomic nerve, the vagus, is usually the first most affected, resulting in the loss of the normal sinus arrhythmia, significant reductions of day-night blood pressure variation, and possibly sudden cardiac death. Nocturnal diarrhea is another consequence of vagal neuropathy.(12) Manifestations include orthostatic or dialysis-associated hypotension, impotence and incontinence.(13)CKD patients may have sympathetic hyperactivity, which contributes to hypertension, accordingly, &- adrenergic blockade has been advocated in CKD.(12)

- **Cranial Neuropathy:** Decreased olfactory function, especially a reduced ability to discriminate among and to identify odors, and dysgeusia are commonly seen in patients with CKD.(3) Bilateral vestibular failure leads to inability to stand or to walk normally without vertigo or nystagmus. It is often related to the use of drugs like aminoglycoside and sulfa based loop diuretics.(4)

Sleep Disorders

Disruption of the sleep–wake cycle is a characteristic feature of uremia, with both excessive daytime sleepiness and insomnia [(14).] Sleep disorders are:

- **Sleep Apnoea:** It is defined as the coexistence of unexplained excessive daytime sleepiness with at least five obstructed breathing events (apnea or hypopnea) per hour of sleep.[(15)] Nocturnal HD significantly reduced the occurrence of sleep apnea.[(16)]

- **Restless Legs Syndrome:** In this syndrome the patient typically complains of a variety of sensory disturbances in the legs, including pins and needles, creeping or crawling sensations, aching, itching, stabbing, heaviness, tension, burning, or coldness. Occasionally, similar symptoms are appreciated in the upper limbs.[(17)] Symptoms occur during periods of inactivity and are alleviated by movement.[(19)] The pathogenesis of this disorder is associated with disrupted dopaminergic function in the brain.[(1)] Iron

deficiency or iron transport into the central nervous system plays a central role in RLS.

- **Periodic Limb Movements of Sleep:** It is a disorder characterized by episodes of involuntary, repetitive extension of the big toe and dorsiflexion of the ankle as well as flexion of the knee and hip. This disorder is more likely to occur in those with RLS.[22]

PATIENTS AND METHODS

This study has been carried out during the period from November 2011 to November 2012, as a cross-sectional for analytic purposes, and enrolled 104 patients with chronic renal failure on regular hemodialysis at the nephrology department of Medical City- Baghdad Teaching Hospital.

Procedure of the Work*:* The study is composed of personal data, taking a full neurological history from the patient, relatives or medical staff and neurological examination, including motor, sensory, cranial nerves and autonomic nervous system by examining the pulse rate during the valsalva maneuver and blood pressure on sitting and standing position and body weight.

- **Investigations:** Blood urea, Serum creatinine, Serum potassium, Serum calcium level, Hemoglobin level, Fasting blood sugar.
- **Variables:** 1. Age.2. Gender.3. BMI.4. Hepatitis state.5. Duration of H. D Hours for dialysis/week.

Inclusion Criteria

- Persons with chronic kidney disease.2. Being on H. D.
- Continue on H. D. for more than a month.4. Age more than 18 years.

Exclusion Criteria

- Being on H. D. for less than a month.
- Age less than 18 years.
- Person history of surgery or trauma that can cause the neurological deficit.
- Persons with D. M have been excluded because many patients with DN also have polyneuropathy. Sensory polyneuropathy is an important aspect of the “diabetic foot.”
- Persons who are taking a drug that can cause neurological abnormality.

Level of Consciousness

Had been assessed in the study by using the Glasgow coma scale as the following: [20]

Motor Score: Eye opening Score

- Obeys 6 points spontaneous opening4 points
- Localizes5 points spontaneous opening 4 points
- Withdraws4 points opening to verbal stimulus3 points

- Abnormal flexion3 points opening to painful stimulus 2 points
- Extensor response2 points nil 1 point

Verbal Score

- Oriented 5 points
- Confused conversation 4 points
- Inappropriate words 3 points
- Incomprehensive sounds 2 points
- Nil 1 point

(Collectively Minimum (3) points and Maximum (15) points)

Valsalva Maneuver

Valsalva maneuver is performed by placing the patient in supine position and instructed to exhale forcefully against a closed glottis after a normal inspiratory effort (i.e., at tidal volume).[23]The expected response in normal subjects is divided into four phases:

- **Phase 1** is characterized by a >15 mmHg rise in the patient's systolic blood pressure that occurs at the onset of the maneuver.
- **Phase 2** is typified by a return of the systolic blood pressure to baseline (below the 15 mmHg increase) during the remainder of the straining phase. Phase 2 occurs due to decreased venous return, the subsequent decrease in stroke volume, and an increase in peripheral vascular resistance, reflex tachycardia occurs during this phase.
- **Phase 3** occurs after release of the strain and is distinguished by an abrupt fall in systolic blood pressure below the baseline.
- **Phase 4** follows and is discerned by a secondary rise in systolic blood pressure >15 mmHg above baseline.[24,25]

In this study phase, 2 is used as a surrogate for autonomic function evaluation by considering the loss of reflex tachycardia as an indicator of autonomic dysfunction. [21]

Postural Hypotension: is also a sign of autonomic dysfunction, which occurs when systolic blood pressure decreased by 20 mmhg or more and diastolic blood pressure decreased by 10 mmhg or more with standing from a sitting position.

Peripheral Neuropathy – is diagnosed [10]

- When the patient complained of at least one of the followings in his extremities: Numbness, pain or burning sensation
- Examination shows a glove and/or stock distribution in at least one of the followings: Decreased reflexes,

decreased the sensation of a pinprick, and decreased light touch.[10]

Mononeuropathy: is diagnosed when the patient complained of pain and/or numbness and there is impaired pinprick, light touch and/or reflexes in dermatomal distribution of a single nerve.[10]

Cranial Neuropathy: is considered [10] when one of the following is present:

- When there is a history of one or more than one cranial nerves involvement.
- When examination shows one or more than one cranial nerves defect.

Autonomic Neuropathy: is considered when there is at least one of the followings:

- Gustatory sweating, nocturnal and/or postprandial diarrhea, postural hypotension and loss of reflex tachycardia by valsalva maneuver.[17]

Periodic Limb Movement: when the patient or partner describe a repetitive jerky movement of a limb during resting or sleeping.[18]

Restless Leg Syndrome: when there is an urge to move a limb after feeling of unpleasant sensation which is relieved by movement.[19]

Muscle weakness: when there is : -

- Proximal myopathy by symptoms of difficulty raising upstairs and combing the hair and examining for Gower sign or focal weakness of upper or lower limbs.
- Clinical examination shows muscle power grade IV or less

Headache: In this is study we are going to consider all types of headache (primary headache disorder, migraine headache, tension-type headache, cluster headache, and paroxysmal hemicranias). [26]

Insomnia: Has not defined not simply by total sleep time, but rather by difficulty in initiation and maintenance of sleep, poor quality of sleep, and an insufficient duration of sleep, such that functioning in the awake state is impaired. [27]

Tremor: Has been divided into fine and flapping tremor.

Reflexes: Have been divided into: normal, diminished and exaggerated reflexes.

Gait: in our study, we divide the patients as having normal gait when they can walk without assistance, partially dependent when they can walk but with aid of an assistant and dependent when they cannot walk at all.

History of **loss of consciousness**, **convulsion** has been recorded

Statistical Analysis

Statistical analyses were done using SPSS version 18.00 computer software (statistical package for social sciences). Frequency distributions for selected variables were done first. An association was considered statistically significant P. of 0.05 or less. Excel version 2010, Chi-square test and Fischer exact test were used for analysis of data. Mean, range and standard deviation have been used also.

RESULTS

The patient number was 104 included in this study. The study showed that the age of the patients was in the range of (18-65 years old) as shown in the table (1), 38 patients were between (18-40) years and 66 patients were between (40-65) years. There were 59 males of the patients and 45 females as shown in table (1), body mass index of the patients was of less than 18.5 m/kg^2 for 67 patients, (18-24.9) m/kg^2 for 24 patients, ≥25 m/kg^2 for 13 patients, 63 patients were negative for hepatitis and the others divided into two groups (23 with HCV and 20 with HBV) as shown in table (1). The period that patients spend on H.D. is between one month and one year for 46 patients and more than one year for 58 patients while patients with less than a month are excluded from the study as shown in the table(1).

Table 1: Demographic Variables

Parameter			
Age	**18-40 y. s**	**>40 y. s**	
	38	66	
Gender	**Male**	**Female**	
	59	45	
BMI	<18.5kg/m	18.5-24.9kg/m	≥25 kg/m
	67	24	13
Hepatitis	**Virus –ve**	**HCV +ve**	**HBV +ve**
	61	23	20
Hemodialysis years	**≥1 year**	**< 1 year**	
	58	46	
Bl. urea	**≥25 mmol/l**	**<25mmol/l**	
	71	33	
S. Cr.	**≥500mmol/l**	**<500mmol/l**	
	76	28	
Hb	**<10 g/dl**	**≥10 g/dl**	
	56	**48**	
S. Ca.	**≤2.1mmol/l**	**>2.1mmol/l**	
	63	41	
S .Po4	**≥2mmol/l**	**<2mmol/l**	
	59	45	
S. K.	**≥5**	**<5**	
	58	46	

The investigations taken for the patients show that 71 patients get bl. Urea of more than 25 mmol/l and 33 patients of less than that, the serum creatinine was more than 500 mmol/l for 76 patients and less than that for 28 patients, 56 patients have PCV<30% and 48 patients have PCV>30%, the serum potassium was more than 5 mmol/l for 58 patients and less than 5 mmol/l for 46 patients, 63 of patients get serum calcium of less than 2.1 mmol/l and 41 of patients get serum calcium of less than that and the serum phosphate level was more than 2 mmol/l for 59 patients and less than that for 45 patients.

The most common neurological symptom of the patients as shown in table(2) was weakness where 46 patients complain of it, followed by a headache in 37 patients then numbness where 36 patients complained of it, there were 28 patients with insomnia, 19 patients with pain at extremities, 15 patients with muscle cramps, 11 patients with postural dizziness, 10 patients with nocturnal and/ or post-prandial diarrhea, 8 patients with periodic limb movement, 7 patients with gustatory sweating, 6 patients with convulsion, 4 patients with restless leg syndrome and no patient complained ofloss of consciousness.

Table 2: Symptoms

Symptom	No. of Patients
Weakness	46
Headache	37
Numbness	36
Insomnia	28
Pain at extremities	19
Muscle cramps	15
Postural dizziness	11
Nocturnal or post-prandial diarrhea	10
Gustatory sweating	7
Periodic limb movements	8
Restless leg syndrome	4
Convulsion	6
Loss of consciousness	0

The neurological signs as shown in table(3) revealed that all the patients have G.C.S. of 15 which is the maximum, 27 patients have fine tremor, 8 patients have flapping tremor, 4 patients have cranial neuropathy, 23 patients have impaired pinprick and light touch sensation in a stock and/or glove distribution while one patient in a dermatomal distribution, 26 patients have proximal myopathy and +ve Gower sign, 11 patients have distal weakness, there was no tone disturbance, 22 patients havehyper-reflexia, 24 patients have decreased reflexes, 8 patients have postural hypotension, 5 patients have loss of tachycardia reflex by valsalva with 4 patients having both signs, gait has been normal in 23 patients while 63 patients is partially dependent and 18 patients are dependent.

Table 3: Signs

Signs	Patient No.		
Abnormal Glascowcoma scale	**Nil**		
Fine tremor	**27**		
Flappingtremor	**8**		
CranialNeuropathy	**4**		
Sensory Signs	**Pin prick and light touch impairment**	**Stock and/or glove dist.**	**23**
		Dermatomal	**1**
Motor Signs	**Decrease muscle power**	**Distal weakness**	**11**
		Proximal myopathy	**26**
	Tonedisturbance	**Nil**	
	Reflexes	**Increased**	**22**
		Decreased	**24**
Autonomic Neuropathy	**Posturalhypotension**		**8**
	Loss of reflex tachycardia by valsalva		**5**
Gait	**Normal**		**23**
	Partially dependent		**63**
	Dependent		**18**

According to the time that the patient spends on hemodialysis the symptoms and signs of the patients are divided into two groups, one for patients with less than one year on H.D. and the second for patients with more than one year as shown in table (4); for the first group the signs and symptoms were as the following; headache in 11 patients, insomnia in 7 patients, convulsion in one patient, fine tremor in 6 patients, flapping tremor in one patient, no one with cranial neuropathy, periodic limb movement in 3 patients, one with restless leg syndrome, distal weakness in 2 patients, proximal

myopathy in 4 patients, muscle cramps in 2 patients, hyper-reflexia in 10 patients, weak/absent reflexes in 4 patients, normal reflexes in 32 patients, peripheral neuropathy in 6 patients, mononeuropathy in one patient, gustatory sweating in 2 patients, post-prandial or nocturnal diarrhea in one patient, postural hypotension in one patient, Abnormal valsalva in one patient and gait is normal in 12 patients while 27 patients are partially dependent and 4 patients are dependent; while for the second group the signs and symptoms were like that; 26 patients complained of a headache, 21 patients had insomnia, 5 patients had convulsion, fine tremor in 21 patients, flapping tremor in 7 patient, 4 patients with cranial neuropathy, periodic limb movement in 5 patients, 3 patients with restless leg syndrome, distal weakness in 9 patients, proximal myopathy in 22 patients, muscle cramps in 13 patients, hyper-reflexia in 12 patients, weak/absent reflexes in 20 patients, normal reflexes in 26 patients, peripheral neuropathy in 37 patients, no one patient mononeuropathy, gustatory sweating in 5 patients, post-prandial or nocturnal diarrhea in 9 patients, postural hypotension in 7 patient, Abnormal valsalva in 4 patients and gait is normal in 11 patients while 36 patients are partially dependent and 14 patients are dependent

Table 4: The Relation between duration on H. D. and Neurological Manifestations

Signs			Patient. No.
Abnormal Glascowcoma scale	**Nil**		
Fine tremor	**27**		
Flappingtremor	**8**		
CranialNeuropathy	**4**		
Sensory Signs	**Pin prick and light touch impairment**	**Stock and/or glove dist.**	**23**
		Dermatomal	**1**
Motor Signs	**Decrease muscle power**	**Distal weakness**	**11**
		Proximal myopathy	**26**
	Tonedisturbance	**Nil**	
	Reflexes	**Increased**	**22**
		Decreased	**24**
Autonomic Neuropathy	**Posturalhypotension**	**8**	
	Loss of reflex tachycardia by valsalva	**5**	
Gait	**Normal**	**23**	
	Partially dependent	**63**	
	Dependent	**18**	

Table(5) shows the correlation between body mass index (dividing the patient as BMI of <18.5kg/m^2 and BMI of 18.6-24.9 kg/m^2 and >25 kg/m^2 and neurological manifestation where headache found in 21 patient with BMI<18.5 kg/m^2 and 9 patient with BMI of 18.6-24.9 kg/m^2 and 7 patient with BMI of >25 kg/m^2, insomnia found in 12 patient with BMI of <18.5 kg/m^2 and 6 patient with BMI of 18.6-24.9 kg/m^2 and 10 patient BMI >25 kg/m^2, convulsion found in 2 patient with BMI <18.5 kg/m^2 and 3 patient with BMI of 18.6-24.9 kg/m^2 and 1 patient with BMI of >25 kg /m^2, fine tremor found in 15 patient with BMI of < 18.5 kg/m^2, 7 patient with BMI of 18.6-24.9 kg/m^2 and 5 patient with BMI of >25 kg/m^2, flapping tremor found in 6 patient with BMI of <18.5 kg/m^2,2 patient with BMI of 18.6-24.9 kg/m^2, no patient with BMI of 18.6-24.9 kg/m^2 and 1 patient with BMI of > 25 kg/m^2, Cranial Nerve involvement found in one patient with BMI of < 18.5 kg/m^2, 2 patients with BMI of 18.5-24.9 kg/m^2 and one patient with BMI of $\geq$25 kg/m^2, restless leg syndrome found in 2 patients with BMI of < 18.5 kg/m^2, one patient with BMI of 18.5-24.9 kg/m^2 and one patient with BMI of $\geq$25 kg/m^2, periodic limb movements found in 3 patients with BMI of < 18.5 kg/m^2, 4 patients with BMI of 18.5-24.9 kg/m^2 and one patient with BMI of $\geq$25 kg/m^2, distal weakness found in 8 patients with BMI <18.5 kg/m^2 and 1 patients with BMI of 18.6 -24.9kg/m^2 and 2 patients of BMI of $\geq$25 kg/m^2, proxy-malmyopathy found in 18 patients with BMI of < 18.5 kg/m^2, 6 patients with BMI of 18.6-24.9kg/m^2 and 2 patients with BMI of $\geq$ 25 kg/m^2, muscle cramps found in 10 patients BMI of

<18.5kg/m^2, 2 patients with BMI of 18.6-24.9 kg/m^2 and 3 patients with BMI of ≥ 25 kg/m^2, hyper reflexia found in 13 patients with BMI of < 18.5 kg/m^2, 5 patients with BMI of 18.6-24.9 kg/m^2 and 4 patients with BMI of ≥ 25 kg/m^2, weak/absent reflexes found in 17 patients with BMI of < 18.5 kg/m^2, 5 patients with BMI of 18.6-24.9 kg/m^2 and 2 patients with BMI of ≥ 25 kg/m^2, normal reflexes found in 38 patients with BMI of < 18.5 kg/m^2, 14 patients with BMI of 18.6-24.9 kg/m^2 and 6 patients with BMI of > 25 kg/m^2, peripheral neuropathy found in 35 patients with BMI of 18.5 kg/m^2, 6 patients with BMI of 18.6-24.9kg/m^2 and2 patients with BMI of ≥ 25kg/m^2, mononeuropathy found in only one patient with BMI of 18.5 kg/m2 and no one in the other groups, postural hypotension found in 7 patients with BMI of 18.5 kg/m^2, no one patient with BMI of 18.6-24.9kg/m^2 and one patient with BMI of ≥ 25kg/m^2, abnormal valsalva found in 5 patients with BMI of 18.5 kg/m^2, no one patient with BMI of 18.6-24.9kg/m^2 and no one patient with BMI of ≥ 25kg/m^2, gustatory sweating found in 3 patients with BMI of <18.5 kg/m^2 and one patient with BMI of 18.6 -24.9kg/m^2 and 3 patient with BMI of ≥ 25kg/m^2, nocturnal / post-prandial diarrhea found in 3 patients with BMI of <18.5 kg/m^2 and 5 patients with BMI of 18.6 -24.9kg/m^2 and 2 patients with BMI of ≥ 25kg/m^2, gait was normal in 10 patients with BMI of <18.5 kg/m^2 and 6 patients with BMI of 18.6 -24.9kg/m^2 and7 patients with BMI of > 25kg/m^2, partially dependent in 48 patients with BMI of <18.5 kg/m^2 and 9 patients with BMI of 18.6 -24.9kg/m^2 and 6 patients with BMI of ≥ 25kg/m^2 and dependent in 15 patients with BMI of <18.5 kg/m^2 and one patient with BMI of 18.6 -24.9kg/m^2 and 2 patients with BMI of ≥ 25kg/m^2.

Table 5: The Relation between Body Mass Index and Neurological Manifestations

system	Findings	BMI(kg/m$^{2)}$	P-value			
		<18.5	18.5-24.9	≥25		
Central nervous system	Headache	21/67(31.3%)	9/24(37.5%)	7/13(53.8%)	0.2	
	Insomnia	12/67(17.9%)	6/24(25%)	10/13(76.9%)	0.09	
	Convulsion	2/67(2.9%)	3/24(12.5%)	1/13(7.69%)	0.61	
	Loss of consciousness	Nil	Nil	Nil		
	Fine tremor	15/67(22.3%)	7/24(29.1%)	5/13(38.46%)	0.45	
	Flapping tremor	6/67(8.9%)	2/24(8.3%)	0/13	0.15	
	Glasgow coma scale	Normal	67/67(100%)	24/24(100%)	13/13(100%)	
		Abnormal	nil	Nil	nil	
Cranial Nerve involvement	1/67(1.49%)	2/24(8.3%)	1/13(7.69%)	0.7		
Restless leg syndrome	2/67(2.9%)	1/24(4.16%)	1/13(7.69%)	0.6		
Periodic limb movements	3/67(4.47%)	4/24(16.6%)	1/13(7.69%)	0.5		
Motor system	Myopathy	Proximal	18/67(26.8%)	6/24(25%)	2/13(15.3%)	0.01
		Distal	8/67(11.9%)	2/24(8.3%)	1/13(7.7%)	0.003
	Muscle cramps	10/67(14.9%)	2/24(8.3%)	3/13(23.07%)	0.14	
	Tendon reflexes	Normal	38/67(56.7%)	14/24(20. 9%	6/13(46.1%)	0.2
		Weak/absent	17/67(23.8%)	5/24(20.8%)	2/13(23.07%)	0.05
		Exaggerated	13/67(19.4%)	5/24(20.8%)	4/13(30.7%)	0.32
Sensory system	Peripheral neuropathy	35/67(52.2%)	6/24(25%)	2/13(15.3%)	0.02	
	Mononeuropathy	1/67(1.49%)	Nil	Nil		
Autonomic neuropathy	Postural hypotension	7/67(10.4%)	Nil	1/13(7.69%)	0.007	
	Abnormal valsalva	5/67((7.47%)	Nil	nil	0.001	
	Gustatory sweating	3/67(2.9%)	1/24(4.16%)	3/13(30.7%)	0.17	
	Nocturnal / post-prandial diarrhea	3/67(4.47%)	5/24(20.8%)	2/13(15.3%)	0.4	

Gait	Normal	10/67(14.9%)	6/24(25%)	7/13(53.8%)	0.12
	Partially dependent	48/67(71.6%)	9/24(37.5%)	6/13(46.1%)	0.02
	Dependent	15/67(22.3%)	1/24(4.16%)	2/13(15.3%)	0.008

As shown in table (6) the patients are classified as being (hepatitis B or C) positive or negative and their symptoms and signs where as the following; headache found in 7 patients with HBV, 10 patients with HCV and 20 patients who are negative for both, insomnia in 8 patients with HBV, 7 patients with HCV and 13 patients who are negative, convulsion in 3 patients with HBV, one with HCV and 2 without virus, fine tremor in 7 patients with HBV, 9 patients with HCV and 11 patients who are negative, flapping tremor in one patient with HBV, 2 patients with HCV and 5 patients without virus, cranial neuropathy in one patient with HBV, 2 patients with HCV and one patient without virus, restless leg syndrome in 2 patients with HBV, one patient with HCV and one patient without virus, periodic limb movement in one patient with HBV, 4 patients with HCV and 3 patients without virus, proximal myopathy in 7 patients with HBV, 6 patients with HCV and 13 patients without virus, distal weakness in 3 patients with HBV, 2 patients with HCV and 6 patients without virus, muscle cramps in 4 patients with HBV, 2 patients with HCV and 9 patients without virus, hyper-reflexia in 6 patients with HBV, 6 patients with HCV and 10 patients without virus, weak/absent reflexes in 3 patients with HBV, 6 patients with HCV and 15 patients without virus, normal reflexes in 11 patients with HBV, 11 patients with HCV and 36 patients without virus, peripheral neuropathy in 9 patients with HBV, 7 patients with HCV and 27 patient without virus, mononeuropathy in only one patient with HCV, gustatory sweating in 2 patients with HBV, 2 patients with HCV and 3 patients without virus, nocturnal or post-prandial diarrhea in 2 patients with HBV, 5 patients with HCV and 3 patients who are negative for both, postural hypotension in 3 patients with HBV, 2 patients with HCV and 3 patients who are negative for both, abnormal valsalva in 1 patients with HBV, 3 patients with HCV and 1 patients who are negative for both, normal gaitin 3 patients with HBV, 8 patients with HCV and 12 patients who are negative for both, partially dependent gait in 12 patients with HBV, 13 patients with HCV and 36 patients who are negative for both, dependent gait in 5 patients with HBV, 2 patients with HCV and 11 patients who are negative for both.

Table 6: The Relation between Hepatitis State and Neurological Manifestations

system	Findings		Hep-ve	Viral Hepatitis		P value
				HCV	HBV	
Central nervous system	Headache		20/61(32.7%)	10/23(43.4%)	7/20(35%)	0.53
	Insomnia		13/61(21.3%)	7/23(30.4%)	8/20(40%)	0.65
	Convulsion		2/61(3.27%)	1/23(4.3%)	3/20(15%)	0.67
	Loss of consciousness		Nil	Nil	Nil	
	Fine tremor		11/61(18.0%)	9/23(39.1%)	7/20(35%)	0.26
	Flapping tremor		5/61(8.19%)	2/23(8.6%)	1/20(5%)	0.71
	Glasgow coma scale	Normal	61/61(100%)	23/23(100%)	20/20(100%)	
		Abnormal	Nil	Nil	Nil	
Cranial Nerve involvement			1/61(1.63%)	2/23(8.6%)	1/20(5%)	0.61
Restless leg syndrome			1/61(1.63%)	1/23(4.3%)	2/20(10%)	0.62
Periodic limb movements			3/61(4.9%)	4/23(17.3%)	1/20(5%)	0.71
Motor system	Myopathy	Proximal	13/61(21.3%)	6/23(26%)	7/20(35%)	1
		Distal	6/61(9.8%)	2/23(8.69%)	3/20(15%)	0.42
	Muscle cramps		9/61(14.7%)	2/23(8.6%)	4/20(20%)	0.4
	Tendon reflexes	Normal	36/61(59%)	11/23(47.8%)	11/20(55%)	0.15
		Weak/absent	15/61(24.5%)	6/23(26%)	3/%)	0.08
		Exaggerated	10/61(16.3%)	6/23(26%)	6/20(7.5%)	0.51
Sensory syem	Peripheral neuropathy		27/61(44.3%)	7/23(30.4%)	9/20(45%)	0.37
	Mononeuropathy		Nil	1/23(4.3%)	Nil	
Autonomic	Postural hypotension		3/61(4.9%)	2/23(8.6%)	3/20(15%)	0.8

neuropathy	**Table 6: Contd.,**				
	Abnormal valsalva	1/61(1.63%)	3/23(13%)	1/20(5%)	0.06
	Gustatory sweating	3/61(4.9%)	2/23(8.6%)	2/20(10%)	1
	Nocturnal / post-prandial diarrhea	3/61(4.9%)	5/23(21.7%)	2/20(10%)	0.18
Gait	Normal	12/61(19.6%)	8/23(34.7%)	3/20(15%)	0.4
	Partially dependent	36/61(59%)	13/23(56.5%)	12/20(60%)	0.07
	Dependent	11/61(18.0%)	2/23(8.6%)	5/20(25%)	0.44

Table(7) show the correlation between hemoglobin level (dividing the patients as having Hb of less 10 g/dl or more or equal to 10 g/dl) and neurological symptoms and signs were as the following headache is present in 24 patients with Hb<10 g/dl, insomnia is found in 12 patients with Hb<10 g/dl and in 16 patients with Hb≥10 g/dl, convulsion in 2 patients with Hb<10mg/dl and in 4 patients with Hb≥10 g/dl, fine tremor found in 15 patients with Hb<10 g/dl and 12 patients with Hb≥10 g/dl, flapping tremor found in 4 patients with Hb<10 g/dl and in 4 patients with Hb≥10 g/dl, cranial neuropathy found in 1 patients with Hb<10 g/dl and in 3 patients ≥10 g/dl, restless leg syndrome found in 3 patients with Hb<10 g/dl and 1 patients with Hb≥10 g/dl, periodic limb movement found in 5 patients with Hb<10 g/dl and 3 patients with Hb≥10 g/dl, proximal myopathy found in 16 patients with Hb<10 g/dl and 10 patients with Hb≥10 g/dl, distal weakness in 5 patients with Hb<10 g/dland in 6 patients ≥10 g/dl muscle cramps found in 9 patients with Hb<10 g/dl and 6 patients with Hb≥10 g/dl, hyper-reflexia found in 9 patients with Hb<10 g/dl and 13 patients with Hb≥10 g/dl, weak/absent reflexes found in 15 patients with Hb<10 g/dl and in 9 patients with Hb>10 g/dl, normal reflexes found in 32 patients with Hb<10 g/dl and in 24 patients with Hb≥10 g/dl, peripheral neuropathy found in 24 patients with Hb<10 g/dl and in 19 patients with Hb≥10 g/dl, mononeuropathy present in one patient with Hb≥10 g/dl, gustatory sweating found in 3 patients with Hb<10 g/dl and 4 patients with Hb≥10 g/dl, nocturnal / post-prandial diarrhea found in 4 patients with Hb<10 g/dl and in 6 patients with Hb≥10 g/dl, postural hypotension found in 6 patients with Hb<10 g/dl and in 2 patients with Hb≥10 g/dl, abnormal valsalva found in 2 patients with Hb<10 g/dl and in 3 patients with Hb≥10 g/dl, normal gait found in 14 patients with Hb<10 g/dl and in 9 patients with Hb≥10 g/dl, partially dependent gait found in 36 patients with Hb<10 g/dl and in 25 patients with Hb≥10 g/dl, dependent gait found in 11 patients with Hb<10 g/dl and in 7 patients with Hb≥10 g/dl.

Table 7: The Relation between Hemoglobin Level and Neurological Manifestations

system	**Findings**		**Hb g/dl**		**P value**
			<10	**≥10**	
Central nervous system	Headache		24//56(42.8%)	13/48(27%)	0.09
	Insomnia		12/56(21.4%)	16/48(33.3%)	0.17
	Convulsion		2/56(3.57%)	4/48(8.3%)	0.53
	Loss of consciousness		Nil	Nil	
	Fine tremor		15/56(26.7%)	12/48(25%)	0.83
	Flapping tremor		4/56(7.1%)	4/48(8.3%)	0.88
	Glasgow coma scale	Normal	56/56(100%)	48/48(100%)	
		Abnormal	Nil	Nil	
Cranial Nerve involvement			1/56(1.78%)	3/48(6.25%)	0.5
Restless leg syndrome			3/56(5.3%)	1/48(2.08%)	0.72
Periodic limb movements			5/56(8.9%)	3/48(6.25%)	0.88
Motor system	Myopathy	Proximal	16/56(28.5%)	10/48(20.8%)	0.36
		Distal	5/56(8.9%)	6/48(12.5%)	0.12
	Muscle cramps		9/56(16%)	6/48(12.5%)	0.6
	Tendon reflexes	Normal	32/56(57.1%)	24/48(50%)	0.32
		Weak/absent	15/56(26.7%)	9/48(18.75%)	0.07
		Exaggerated	9/56(16%)	13/48(27%)	0.17

Table 7: Contd.,				
Sensory syem	Peripheral neuropathy	24/56(42.8%)	19/48(39.5%)	0.44
	Mononeuropathy	Nil	1/48(2.08%)	
Autonomic neuropathy	Postural hypotension	6/56(10.7%)	2/48(4.1%)	0.04
	Abnormal valsalva	2/56(3.57%)	3/48(6.25%)	0.11
	Gustatory sweating	3/56(5.3%)	4/48(8.3%)	0.83
	Nocturnal / post-prandial diarrhea	4/56(7.1%)	6/48(12.5%)	0.55
Gait	Normal	14/56(25%)	9/48(18.75%)	0.8
	Partially dependent	36/56(64.2%)	25/48(52%)	0.41
	Dependent	11/56(19.6%)	7/48(14.5%)	0.2

DISCUSSIONS

Our study had been done on patients with chronic kidney disease on hemodialysis, during which, 104 patients taken showing that CKD occur more commonly after the age of forty, similar to the results of Albbashir H. and et al. Study from Sudan in 2010 where 300 patients included showing the mean age of patients was 55.92 years [(28)]and similar to the results of Güven K. and et al. From Turkey in 2007 where the mean age was 54.6 years of 109 hemodialysis patients, this distribution can be due to increased prevalence of renal impairment in elderly, increased survival on hemodialysis and increased efficacy and more developed instrumentations for creation of vascular access even in the elderly.[(29)]

In the study as shown in table (1) we have (56.8%) males and (43.2%) females while in Sudan Albbashir H. had a male to female ratio of 2:1 [(28)]and Nemanja Jonić from Serbia at 2008 showed that from overall number of patients included, (67.2%)of the men and (32,9%) women,[(30)] patterns in the incidence of kidney disease across gender are generally consistent, with higher rates occurring in men than in women. Similarly, men are reported to have greater rates of progression of non-diabetic CKD for some specific types of kidney disease, especially compared with premenopausal women. More investigation into rates of progression of IgA nephropathy, lupus nephritis, and ADPKD across gender and into overall progression rates in postmenopausal women is warranted. Additional study of the effects of HRT in women on the incidence and progression of kidney disease is also needed. [(1)] However, the difference in the ratio between our country and others occurred because of social issues that renal transplantation is done for males more than that for females.

In our study the most common neurological symptom was weakness and during the examination the proximal myopathy > distal weakness whereas in Sudan by Albbashir H. and et.al. the proximal myopathy also higher than distal weakness, but lower figure, this can be due to uremia, electrolyte disturbance, metabolic bone disease, anemia or as a part of peripheral neuropathy.[(28)]The second most common symptom was a headache and it can be due to changes in blood pressure, mild uremic encephalopathy or disequilibrium syndrome, anemia, tension headache or a migraine headache.[(2,31)]

In our study insomnia found in about (30%) of the patients which was lower than that of Parker KP study who said that insomnia presented in 50% of hemodialysis patients,[(49)]Sleep disorders (i.e., sleep apnea, RLS, and periodic limb movements of sleep) have been correlated with complaints of insomnia in some but not all studies, and therefore other factors associated with uremia, such as altered melatonin metabolism, or disrupted regulation of body temperature related to use of dialysate fluid, have been suggested as potential etiologic mechanisms.[(17)]Restless leg syndrome and periodic limb movement was found in about 10% of our patients similar to the result by Hogl B. et al. The cause of RLS is primary (or idiopathic) or secondary to a number of disorders, including iron deficiency, uremia, diabetes mellitus, rheumatic disease, and venous insufficiency, among others while PLM has unknown causes. [(32)]

In our study the convulsion presented in a lot of this can be due to Uremic encephalopathy, Dialysis disequilibrium syndrome, drugs such as erythropoietin, hemodynamic instability, whether hypotension or hypertension, cerebrovascular disease, such as hypertensive encephalopathy, infarction, hemorrhage, and subdural hematoma, electrolyte disorders, such as hypercalcemia, hypocalcemia, hypoglycemia, hyperglycemia, hyponatremia, and hypernatremia, alcohol withdrawal and air embolism.[33]Muscle cramps found in (15%) of our patients and was lower than the percentage of Canzanello et al. At where (30%) of patients complained of muscle cramps,[34] this low percentage can be due to increasing awareness and be using more careful dialysis and preventive measures. The percentage of patients who having one or more of symptoms or signs of peripheral neuropathy were about (40%) patients and signs of mononeuropathy in only one patient, Galassi G.et al at 1998 discovered that nerve conduction abnormalities have been reported in up to 60% of patients receiving dialysis, this can occur due to electrolytes abnormality, malnutrition, and the chronic inflammatory process.[50] The large variation here because we have depended on a clinical exam by eliciting physical signs, but in the other study had depended on nerve conducting velocity and muscle active potential, which is more sensitive.

Autonomic neuropathy in our study (postural dizziness, post-prandial or nocturnal diarrhea, gustatory sweating, and loss of reflex tachycardia by valsalva maneuver)were lower than other studies (Orofino L. et al. at 1990 [35]and Ewing DJ et al. at 1975[36]) and this difference can be due to decreased threshold for starting dialysis and improved efficacy of dialysis over the years.

Reflexes were increased in about 20%and tremor in 8% of patients which can be due to electrolyte abnormality or uremic encephalopathy, drugs and organ failure. [2]Gait disorder was abnormal in about 80% of patients (whether partially dependent or dependent), just like what was shown in a study of Sakkas GK et al. from California in USA at2004.[37]Gait disorders can be caused by sensory deficits, myelopathy, multiple infarcts, parkinsonism, cerebellar degeneration, hydrocephalus, psychogenic and toxic/metabolic.[38]

In our study we found that neurological manifestations were more prominent in patient whose spending more than one year on hemmdialysisthan whose spending less than one year and the differences were statistically significant, which means hemodialysis did not correct most of the neurological disorders and they can start while patient on dialysis due to either the presence of substances not removed by hemodialysis which are toxic to neurological system or hemodialysis is not adequate, A switch to a high-flux membrane or hemodiafiltration to increase the removal of middle molecules may be of benefit, also, more frequent hemodialysis, and especially six times per week nocturnal hemodialysis, may improve neuropathy,[5] hemodialysis per se can cause toxicity to neurological system due to chronic inflammatory process[39] and nutrients are lost into the dialysate,[40] Pyridoxine supplementation has been reported to improve peripheral polyneuropathy in a group of elderly Japanese dialysis patients.

In our study, we found that about 2/3 of patients had low BMI (<18.5kg/m^2)and it is comparable to study of Roberto Marce´n et al. from Spain at 1997 who studied 761 patient on HD showing that; 80% of patients had some degree of malnutrition.[41] in all studies patients on hemodialysis have low body mass index due to multiple factors which are the presence of an acute, chronic or occult systemic illness leading to an inflammatory response may adversely impact nutritional status, markedly increased energy expenditure, proinflammatory cytokine levels, and oxidative stress appear to provide a link between inflammation and malnutrition.[39]Nutrients are lost into the dialysate, as an example, amino acid losses into dialysate can reach 4 to 6 g/day with hemodialysis,[40] dietary restrictions can make food less palatable,

furthermore, the encouragement to restrict fluid intake to minimize intradialytic weight gain may lead to a concurrent decrease in caloric intake,[42]persistent metabolic acidosis may enhance protein degradation and amino acid oxidation,[43] Some medications, such as phosphate binders, can impair nutrient absorption, Adequate dialysis is not a complete substitute for the clearance functions of an intact kidney, in particular, the retention of middle molecules (1000 to 5000 Daltons) may in part contribute to anorexia, possibly by directly affecting the central nervous system,[44] Serum concentrations of leptin, a hormone that induces satiety via effects upon the hypothalamus, may be increased due to reduced renal or dialysis clearance.[45]In our study the neurological manifestation were more prominent in patients of BMI<18.5kg/m^2 and the difference was statically significant which may be related to vitamins, nutrients and minerals deficiency that can disturb neurological functions, also protein deficiency causes alteration in neurotransmitter levels because dietary amino acids play aprecursor role in neurotransmitter synthesis (tyrosine for norepinephrine and tryptophan for serotonin) and their turnover decreases with protein deficiency[46] and because glucose acts as a precursor to acetylcholine, low glucose availability to the brain is associated with cognitive decline, especially verbal learning and short term memory[47].The presence or absence of hepatitis or anemia had no significant effect on the neurological manifestation as shown in our study, except for postural hypotension which is more common in patients with Hb<10 g/dl. Cronin H. at November 2010 stated that anemia one of the common causes of postural hypotension.[48]

CONCLUSIONS

Neurological disorders are common among patients on hemodialysis where weakness was the most common symptom and fine tremor was the most common sign. Most of the patients enrolled in the study had partially dependent gait. The duration that the patient is on hemodialysis has a negative impact, and the neurological symptoms like headache, insomnia, fine tremor, proximal myopathy, distal myopathy, muscle cramps, weak/absent reflexes, peripheral neuropathy, postural hypotension, abnormal valsalva, nocturnal/post-prandial diarrhea and dependent gait were more common in patients whose spent more than one year on hemodialysis and the difference was statistically significant. The body mass index can affect some of the neurological manifestations and our study shows that there was a statistically significant difference in proximal weakness, distal weakness, weak/absent reflexes, peripheral neuropathy, postural hypotension, abnormal valsalva, dependent gait and partially dependent gait which are presented more in patients with BMI < 18.5 kg/m^2. Patients with anemia (Hb<10 gm/dl)had more postural hypotension than those with (Hb>10 gm/d) and the difference statistically was significant while other neurological manifestations not. The hepatitis state of the patient has no impact on the neurological manifestations of the patients.

RECOMMENDATIONS

- The duration that the patients spent on hemodialysis is an important factor in worsening neurological impairment (the more time on hemodialysis the more neurological impairment); so, we have to refer the patient to transplantation as early as possible because transplantation can prevent and sometimes reverse some of the neurological complications of renal failure.
- Measuring body mass index and informing all patients on hemodialysis about dieting to keep their BMI as typical as possible to prevent malnutrition, vitamins and nutrients deficiency and their negative effects on the neurological system.
- Meticulous attention has to be directed toward electrolyte levels in patients on hemodialysis to be corrected.

- We need to investigate for toxins that can cause neurological impairment (apart from known toxins) that cannot be removed by hemodialysis.
- Increase hours of hemodialysis to at least 12 hours per week for all patients to optimize their general wellbeing and decrease their toxins level.
- Investigate for the possibility that hemodialysis membranes may induce a state of chronic inflammation and to find solutions.
- Search for causes of renal failure in all patients on chronic hemodialysis and their impact on the nervous system.

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